Dermatoses of Pregnancy

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Disclosures

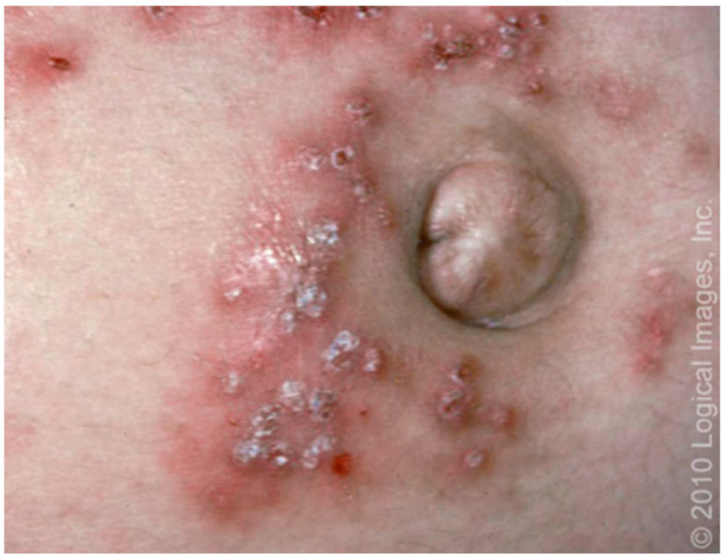
- I am on the board of directors for the Hidradenitis Suppurativa Foundation
- I have served as an advisor for Novartis, UCB, and Boehringer Ingelheim and as a speaker and advisor for AbbVie
- Will discuss off-label uses of medications

5 Dermatoses of Pregnancy

- Pemphigoid gestationis (PG)
- Polymorphic eruption of pregnancy (PEP)
  - Pruritic urticarial papules and plaques of pregnancy (PUPPP)
- Atopic eruption of pregnancy (AEP)
  - Eczema in pregnancy, prurigo of pregnancy, pruritic folliculitis of pregnancy
- Intrahepatic cholestasis of pregnancy (ICP)
- Pustular psoriasis of pregnancy

Key Points for Dermatoses of Pregnancy

- Epidemiology
- Pathogenesis
- Clinical presentation
- Differential diagnosis
- Work-up
- Maternal risk/Fetal risk
- Risk of recurrence with subsequent pregnancy
- Treatment

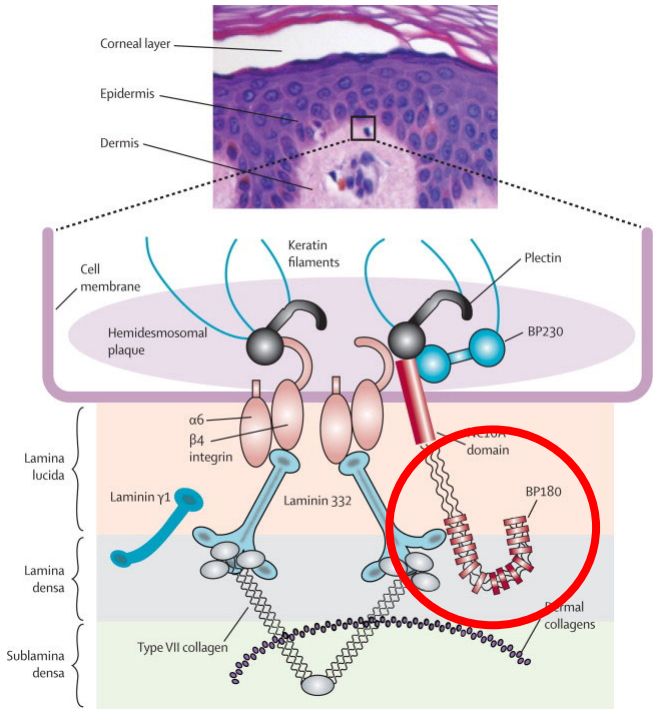


UpToDate

Pemphigoid Gestationis

- Incidence: 1 in 20-50,000 pregnancies
- Trimester: 2nd or 3rd (late in pregnancy)
- Pathogenesis: Unclear
  - Antibodies against 180 kDa transmembrane hemidesmosomal protein (BPAg2 or collagen XVII), the NC16A segment.
  - Patients who express MHC class II HLA antigens DR3 and DR4 are predisposed to developing this disease.

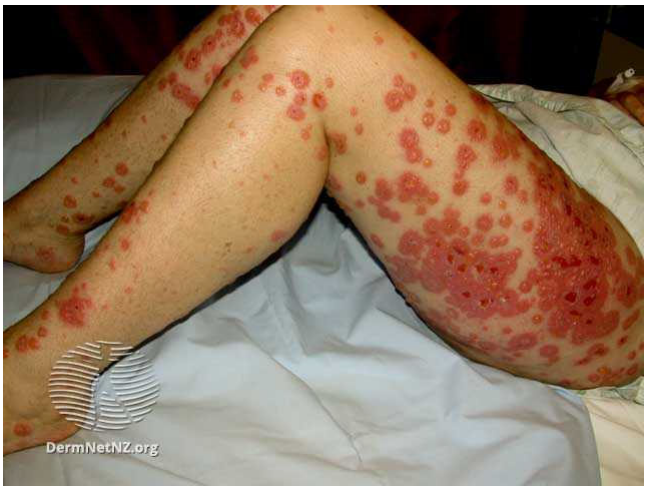
Sadik et al., Clin. Dermatology, 2016



Schmidt and Zillikens, The Lancet, 2013

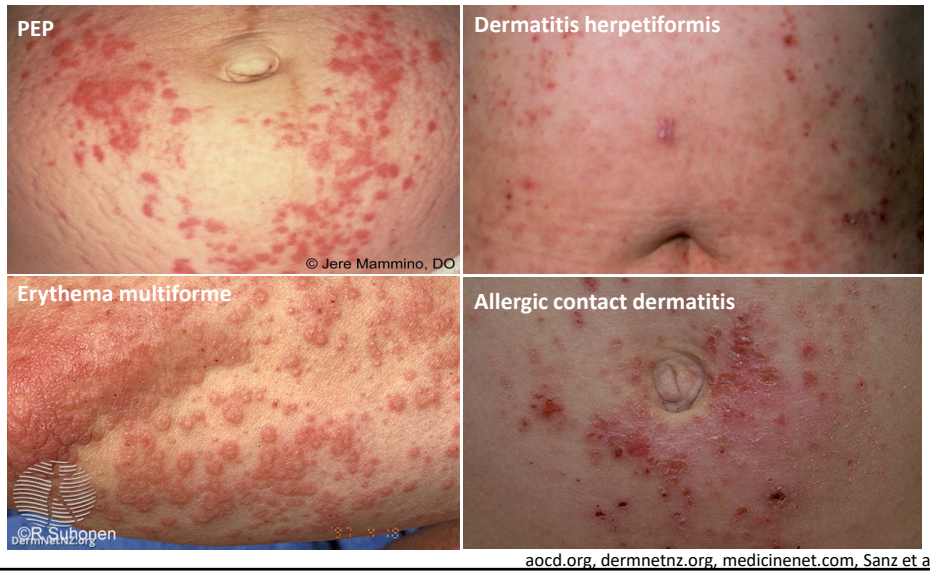
Pemphigoid Gestationis

- Abrupt onset of inflammatory skin lesions
- Can be polymorphic (erythematous papules and plaques, erythema multiforme–like or eczematous lesions, papulo-vesicles, bullae)
- Erupts around umbilicus, spreads to abdomen and extremities
- Typically spares the face, mucous membranes, palms and soles.



Dermnetnz.org

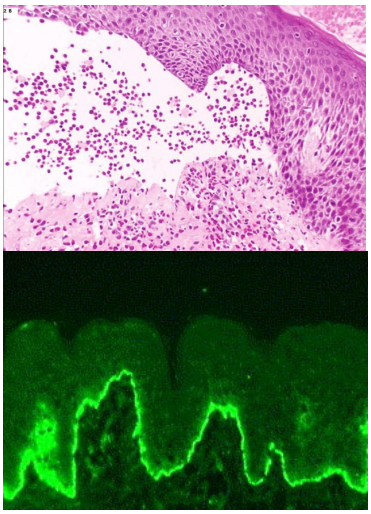
Pemphigoid Gestationis



aocd.org, dermnetnz.org, medicinenet.com, Sanz et al. OmniaScience 2022

Pemphigoid Gestationis

- Histopathology
  - Papillary edema, eosinophilic spongiosis, inflammatory infiltrate of eosinophils and lymphocytes. Subepidermal split in later stages.
- DIF: Linear deposition of C3 and IgG along the basement
- IIF: Detection of circulating IgG antibodies for the BMZ
- ELISA: IgG antibodies against BP180
- C4d immunohistochemistry (potential marker)
  - One 2013 study found C4d deposition along BMZ in 100% (8/8) PG cases and 0/11 PEP cases



Sadik et al. Clin. Dermatology, 2016
Cobo et al. Clinics, 2009; Castro et al, JAAD, 2006

Pemphigoid Gestationis

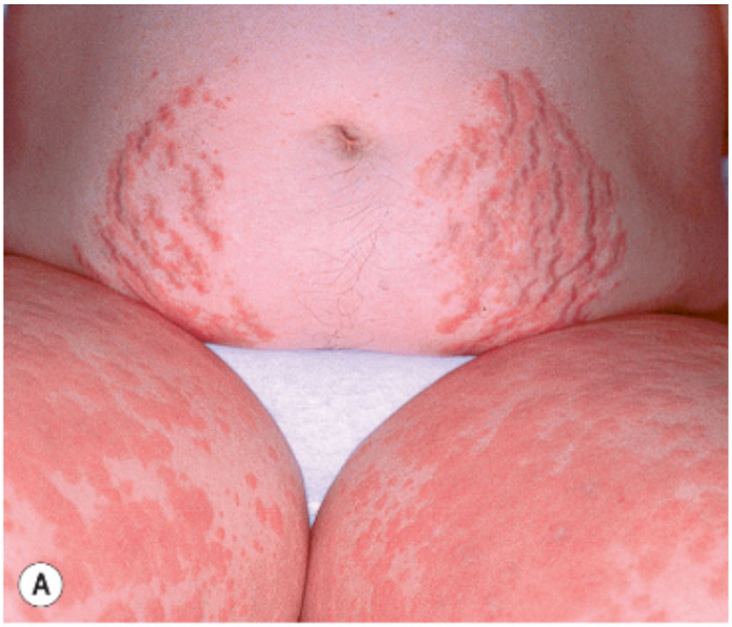
- Clinical Course
  - Mostly self-limiting
  - Symptoms usually disappear completely by 6 months postdelivery
- Maternal risk:
  - In less than 5% of cases, PG becomes chronic and indistinguishable from BP
- Fetal risk:
  - Slightly increased risk for prematurity and small-for-gestational age babies
- Recurrence risk with subsequent pregnancy:
  - Recurs in 90% of all cases in subsequent pregnancies and often with aggravated severity

Sadik et al. Clin. Dermatology, 2016

Pemphigoid Gestationis

- Treatment
  - High potency topical steroids if localized
  - Prednisone/Prednisolone 0.25 to 0.5 mg/kg
  - Consider IVIG +/- immunosuppressants such as cyclosporine or azathioprine
  - Consider immunoadsorption
- Post-partum treatment
  - IVIG, azathioprine, cyclosporine, cyclophosphamide, doxycycline, nicotinamide, dapsone, rituximab
- Pruritus control
  - Oral antihistamines – diphenhydramine, cetirizine, etc.

Sadik et al. Clin. Dermatology, 2016



Bolognia's *Dermatology,* 4e

Polymorphic Eruption of Pregnancy

History:

- 1962: Bourne's "toxemic rash of pregnancy"
- 1968: Nurse's "late onset prurigo of pregnancy"
- 1977: Lawley clarified PUPPP to be synonymous with above two entities
- 1982: Holmes suggested the term "toxic erythema of pregnancy" and then later proposed the title "polymorphic eruption of pregnancy"

Polymorphic Eruption of Pregnancy

- Incidence: 1 in 120-200 pregnancies
- Trimester: 3rd (late in pregnancy) or shortly post-partum
- More common in settings of primigravida women, multiple gestation pregnancies, and male fetus

Taylor et al. Clin. Dermatology, 2016
Brandão et al. Journal of Obstetrics and Gynaecology, 2017

Polymorphic Eruption of Pregnancy

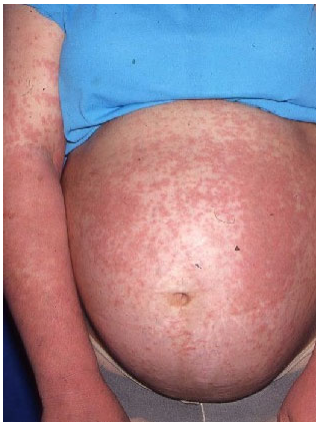
Pathogenesis remains elusive. Select theories include:

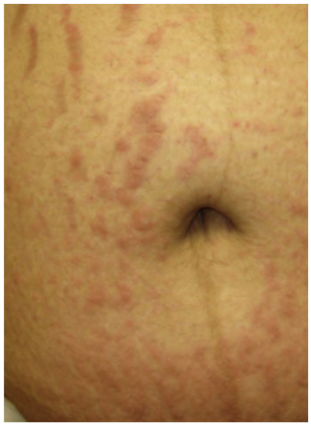
- Skin stretching
  - Skin stretching damaged connective tissue and exposes dermal antigens
- Immunologic response to circulating fetal antigens
  - Fetal male DNA has been found in the skin lesions of PEP patients
- Hormonal:
  - PEP lesional skin with progesterone receptor immunoreactivity that is not seen in non-lesional skin
  - Progesterone level increased in multiple gestation pregnancy and may increase inflammation

Taylor et al. Clin. Dermatology, 2016
Brandão et al. Journal of Obstetrics and Gynaecology, 2017

Polymorphic Eruption of Pregnancy

- Predominant abdominal involvement, often beginning within and around striae
- Pruritic, urticarial papules and plaques
- May include small vesicles or erythema multiforme–like targetoid lesions
- Rare involvement of palms/soles with papules/vesicles resembling dyshidrotic eczema (<2%)

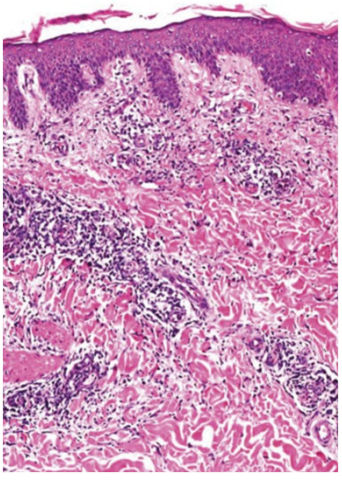




Sävervall et al. Dermatol Res Pract. 2015; Taylor et al. Clin. Dermatology 2016.

Polymorphic Eruption of Pregnancy

- Histopathology (non-specific):
  - Superficial (+/- deep) perivascular lymphocytic infiltrate
  - Eosinophils to varying degrees
  - May see lymphocytic vasculitis
  - Sometimes focal spongiosis, parakeratosis
- DIF negative
  - Differentiates PEP from PG



Massone et al. Am J Dermatopathol. 2014

How to Distinguish PEP from PG

- **Clinically differentiate:**
  PEP tends to spare the umbilicus, usually affects primigravidas and those with a multiple gestation pregnancy

- **Work-up to differentiate:**
  DIF of peri-lesional skin or ELISA of BP180 IgG

Polymorphic Eruption of Pregnancy

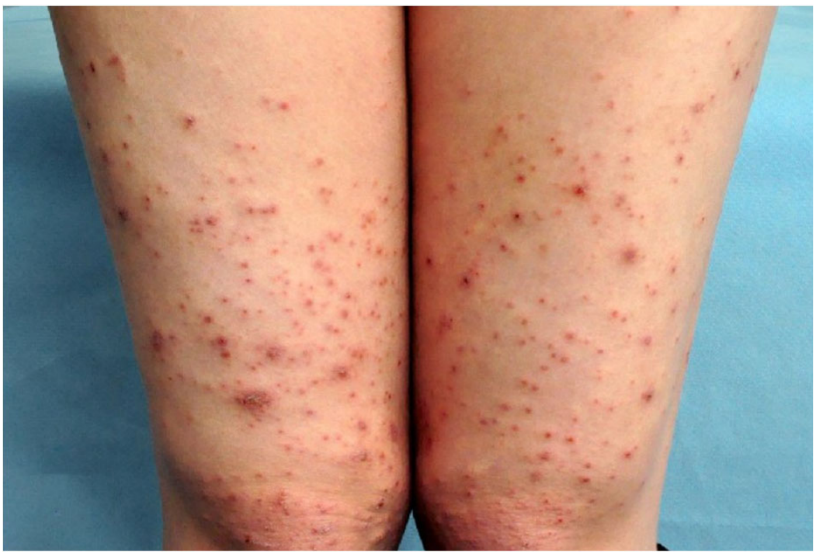
- Clinical Course: Typically self-limited to 4-6 weeks
  - May persist for several weeks postpartum
- Maternal risk: Possible increased incidence of c-section
- Fetal risk: None
- Recurrence risk with subsequent pregnancy: Rare

Taylor et al. Clin. Dermatology, 2016

Polymorphic Eruption of Pregnancy

- Symptomatic treatment
  - Oral first-generation sedating antihistamines
  - Topical steroids
  - Cooling baths, emollients, menthol-containing topicals, light cotton clothing
- Severe cases may warrant systemic steroids
  - Prednisone 40-60mg (0.5 mg/kg) daily for 7 days then tapered over 1-2 weeks
- Narrowband UVB has also been reported as effective

Taylor et al., Clin. Dermatology, 2016



Sävervall et al. Dermatol Res Pract. 2015

Atopic Eruption of Pregnancy

Includes:

- Besnier (1904): Prurigo gestationis
- Spangler (1962): Papular dermatitis of pregnancy
- Nurse (1968): Early-onset prurigo of pregnancy

Also known as:

- Pruritic folliculitis of pregnancy
- Atopic eczema in pregnancy

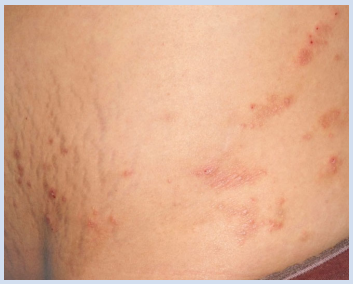
Atopic Eruption of Pregnancy

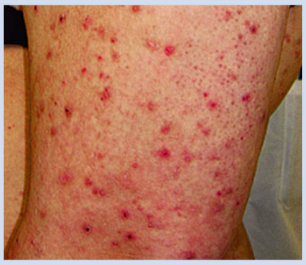
- Incidence: 1 in 5-20 pregnancies
  - Most common pregnancy dermatosis
  - 20% of patients: exacerbation of preexisting atopic dermatitis
  - 80%: experience dermatitis for the first time/after long remission
- Trimester: 75% before 3rd trimester
- Pathogenesis: Unclear.
  - Thought to be triggered by pregnancy-specific immunological changes
  - During pregnancy, increased Th2 cytokine (IL-4 and IL-10) production

Sävervall et al. Dermatol Res Pract, 2015

Atopic Eruption of Pregnancy

E-TYPE 2/3 of patients	P-TYPE 1/3 of patients
• Eczematous dermatitis • Classic atopic sites (antecubital and popliteal fossae, face, eyelids, and neck)	• Erythematous, excoriated nodules/papules • Extensor surfaces of the limbs and trunk • Includes pruritic folliculitis of pregnancy





Dermcoll.edu.au; UpToDate

Atopic Eruption of Pregnancy

- Work-up: Generally not indicated
  - Elevated serum IgE in 20-70%
  - If pustule present, consider culture to r/o folliculitis 2/2 bacteria or fungus/yeast
  - Consider skin biopsy if ruling out PG
- Histopathology: Nonspecific
  - Spongiosis and a perivascular mononuclear infiltrate
- DIF and IIF negative

Vaughan Jones et al. Br J Dermatol, 1999
Ambros-Rudolph et al. JAAD, 2006

Atopic Eruption of Pregnancy

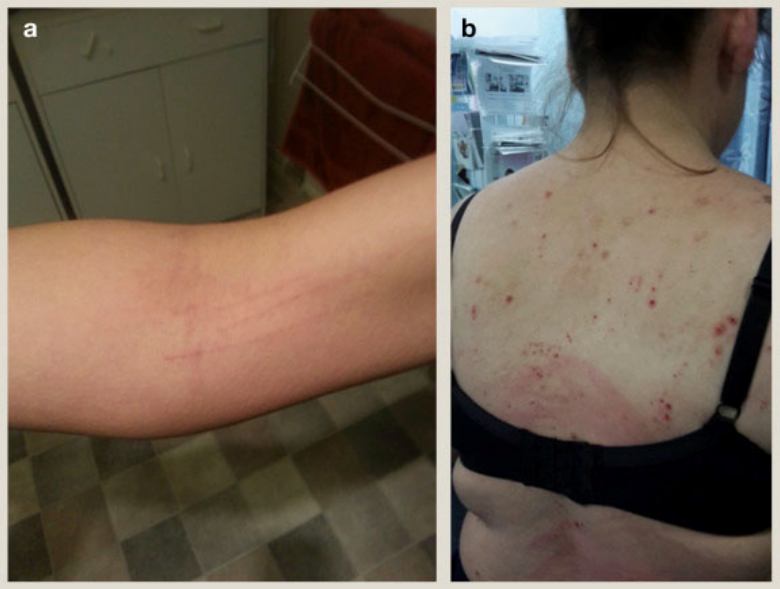
- Maternal risk: None
- Fetal risk: None
- Recurrence risk with subsequent pregnancy: Variable

Lehrhoff et al. Dermatologic Therapy, 2013

Atopic Eruption of Pregnancy

- Treatment: Symptomatic relief
  - Emollients, lukewarm showers, mild soaps, hypoallergenic detergents, soft fabrics
- Low to mid potency topical steroids
- First-generation antihistamines for pruritus
- Narrow-band UVB may be used in severe cases
- Consider short trial of prednisone in recalcitrant and highly symptomatic cases

Lehrhoff et al. Dermatologic Therapy, 2013



Chivers et al. Obstetrics, Gynaecology & Reproductive Medicine, 2018

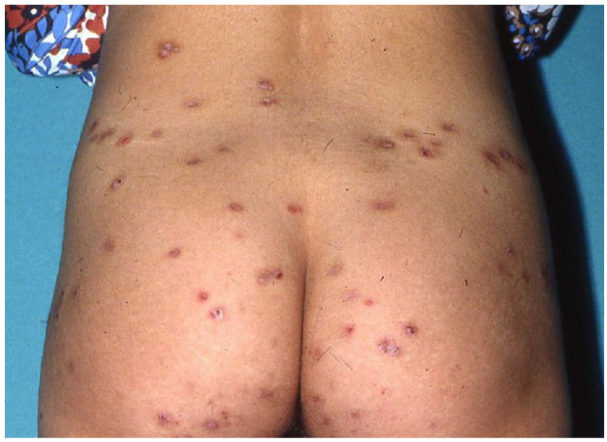
Intrahepatic Cholestasis of Pregnancy

- Incidence: Around 1%, but varies widely with geographic variation
  - 5.6% in a primarily Hispanic population in Los Angeles, CA
  - 27% among Araucanos Indians in Chile
- Trimester: 3rd (late in pregnancy)
- Pathogenesis: Not completely understood
  - Estrogen may reduce bile acid uptake into hepatocytes
  - Small subset have underlying liver disease (i.e. hep C, nonalcoholic liver cirrhosis)
  - Genetic susceptibility suggested due to familial clustering, increased risk in some ethnic groups, and high recurrence rate
  - Mutations in the ABCB4 (adenosine triphosphate-cassette transport B4) gene, which encodes transport proteins involved in bile excretion

Lee et al. J Perinatol, 2006
Ropponen et al. Hepatology, 2006
Sävervall et al. Dermatol Res Pract. 2015

Intrahepatic Cholestasis of Pregnancy

- Generalized pruritus, includes palms, soles, typically worse at night
- Skin lesions vary from minor excoriations to prurigo nodules
- Up to 25% of patients develop jaundice, typically 1-4 weeks after onset of pruritus



Sävervall et al. Dermatol Res Pract. 2015

Intrahepatic Cholestasis of Pregnancy

- Pregnancy-specific causes of pruritus
  - Pruritus gravidarum
  - AEP, PEP, PG
- Pregnancy-specific causes of hepatic impairment
  - Acute fatty liver of pregnancy
  - Hyperemesis gravidarum
  - HELLP
- Pre-existing causes of hepatic impairment
  - Viral, autoimmune, PBC/PSC, drug-induced
  - Biliary obstruction

Williamson and Geenes, Obstetrics & Gynecology, 2014

Intrahepatic Cholestasis of Pregnancy

- Work-up:
  - Elevated total bilirubin (>90% of cases)
  - Elevated AST and ALT (~60% of cases)

Intrahepatic Cholestasis of Pregnancy

- Clinical course: Persists until delivery, then resolves over 2-3 weeks
- Maternal risk:
  - Increased risk of bleeding problems if malabsorption of vit K
  - Potential association with increased risk of gestational DM and pre-eclampsia
  - May be associated with subsequent diagnosis of hepatobiliary disease, including gallstones, cholangitis, hepatitis C, and cirrhosis
- Fetal risk:
  - Increased risk of stillbirth, preterm delivery, NICU admission
  - Majority of stillbirths tend to occur at the 38th week
  - Women with ICP and markedly elevated serum bile acids (>40 µmol/L) should be considered for delivery at 37 weeks or earlier
- Recurrence risk with subsequent pregnancy: High (45% to 70%)

Lehrhoff et al. Dermatologic Therapy, 2013

Intrahepatic Cholestasis of Pregnancy

- Ursodeoxycholic acid
  - 300 mg three times a day (or 15 mg/kg per day) until delivery or 300 mg twice daily (or 10 mg/kg per day)
- In refractory cases,
  - S-adenosyl-methionine (SAMe)
  - Cholestyramine
  - Rifampin
- Antihistamines for pruritus
- Monitor prothrombin time and give vitamin K if needed
- Early delivery if warranted

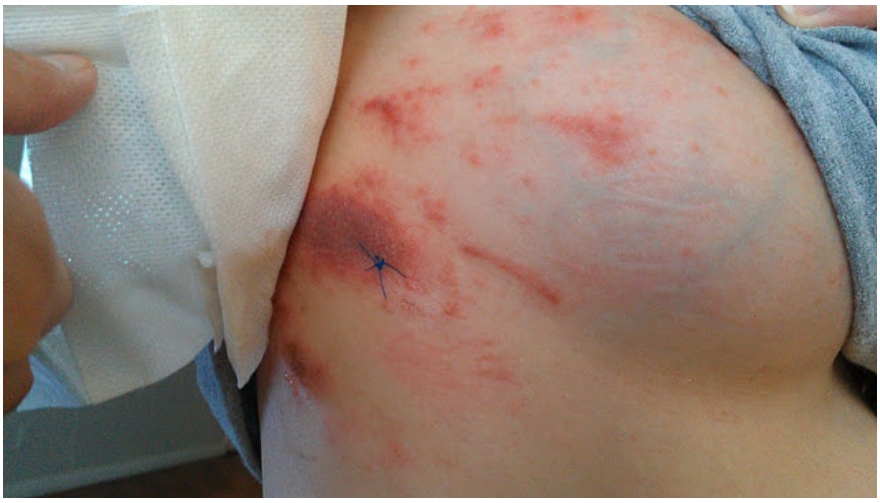
Bechtel and Plotner, Clin Obstet Gynecol, 2015

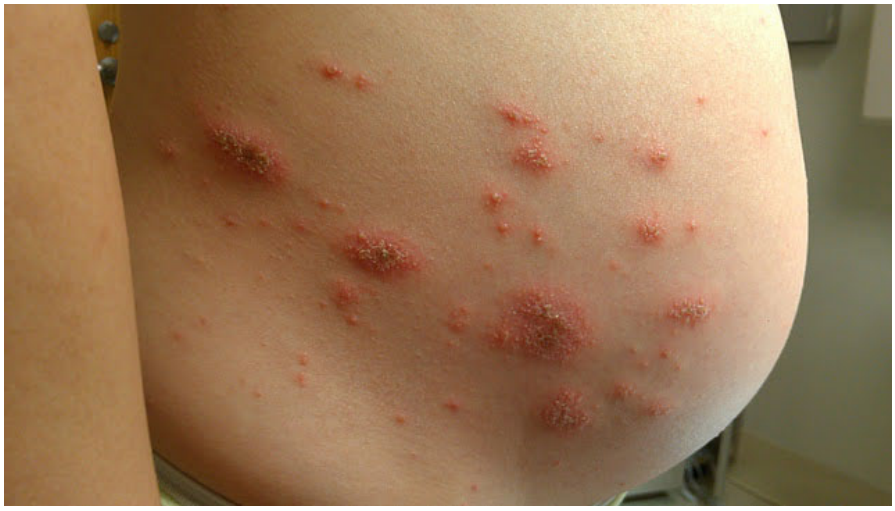
Case Study

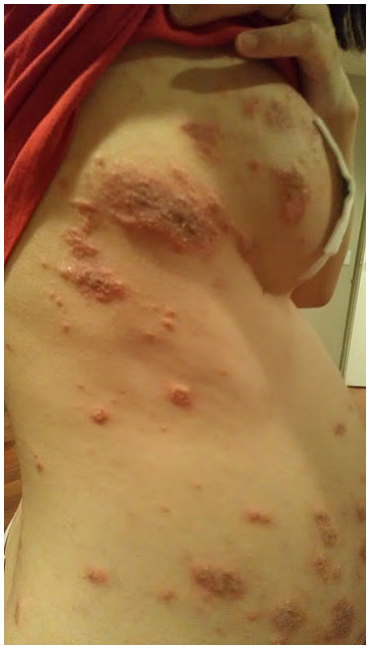
- A 36 yo G1P0 woman presented at 24 weeks 6 days with an 8-week history of a progressive truncal rash.
- The rash began as a single slowly enlarging plaque on her right lateral chest wall that was pruritic.
- She then developed intensely pruritic scattered red pustular lesions on her lower abdomen which spread to involve her chest, neck, back, arms, hands and legs.

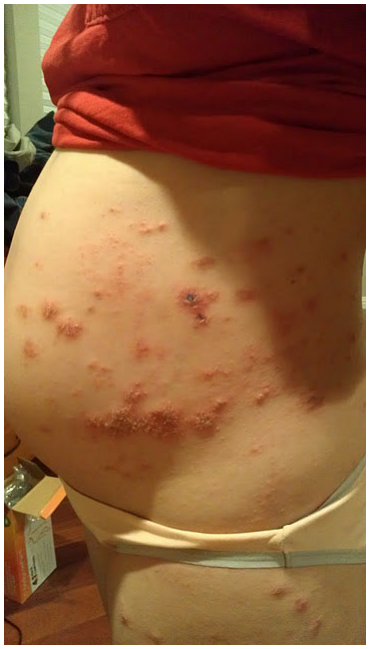
Case Study

- Hydrocortisone cream and Benadryl po provided limited symptomatic relief.
- ROS negative for systemic symptoms
- No personal or family history of psoriasis, eczema, allergic rhinitis or asthma.
- Meds: Prenatal vitamins









Differential Diagnosis

- Pemphigoid gestationis
- Impetiginized eczema
- Drug eruption
- Pustular psoriasis of pregnancy (impetigo herpetiformis)

Histopathology

- Erythematous plaque on her right lateral trunk: Spongiotic psoriasiform dermatitis with superficial peri-vascular and interstitial mixed inflammation with scattered eosinophils.
- Plaque on her left abdomen: Spongiotic psoriasiform dermatitis with subcorneal pustule formation, consistent with pustular psoriasis.
- DIF negative.
- Cultures negative for bacteria or fungi.
- **Dx: Impetigo herpetiformis**

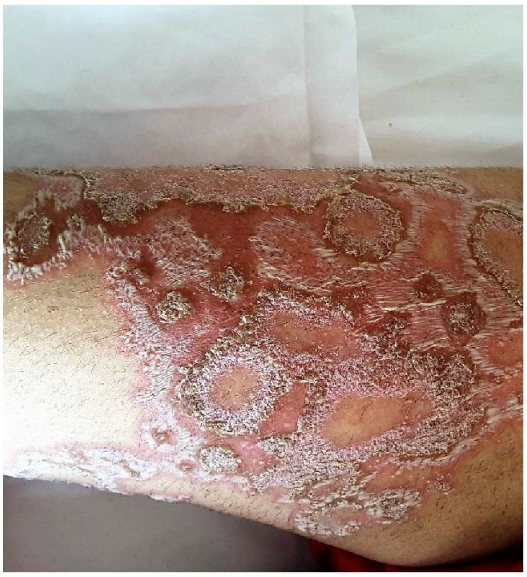
Impetigo Herpetiformis

- Now widely considered a subtype of generalized pustular psoriasis occurring during pregnancy.
- Incidence: Rare
- Trimester: 3rd
- Pathophysiology: Unclear
  - May carry a mutation in IL-36 receptor antagonist (IL36RN) gene
  - Associated with hypocalcemia/hypoparathyroidism

Namazi and Dadkhahfar, Dermatol Res Pract. 2018

Impetigo Herpetiformis

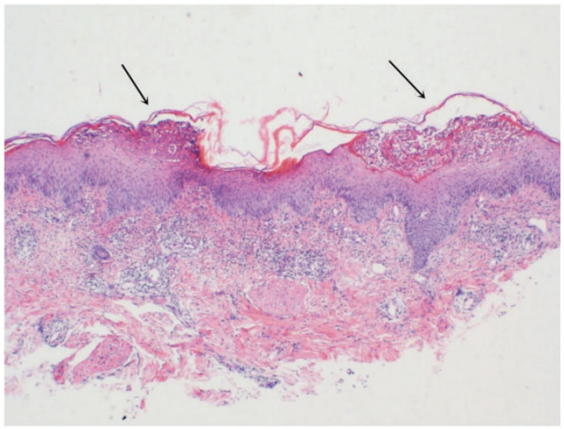
- Erythematous patches with marginal grouped sterile pustules, primarily in flexural regions, may develop erosion/crust or become impetiginized.
- Rarely, nail involvement or oral or esophageal erosions.



Namazi and Dadkhahfar, Dermatol Res Pract. 2018

Impetigo Herpetiformis

- Work-up
  - CBC (leukocytosis with increased neuts), elevated ESR, low calcium, phosphate and vitamin D levels (from hypoparathyroidism), low albumin
  - Culture pustules to rule out bacteria, yeast
  - Biopsy for confirmation
    - Histology: Subcorneal neutrophilic pustules
  - DIF/IIF: negative



Roth, Am J Clin Dermatol. 2011
Yao et al, Int Medical Res. 2020

Impetigo Herpetiformis

- Clinical course: Typically resolves quickly postpartum
- Maternal risk: Good prognosis; avoid complications from hypocalcemia with early recognition and treatment
- Fetal risk: Increased risk of stillbirth, neonatal death, and fetal abnormalities
- Recurrence risk with subsequent pregnancy: May occur in subsequent pregnancies

Namazi and Sadkhahfar, Dermatol Res Pract. 2018
Roth, Am J Clin Dermatol. 2011

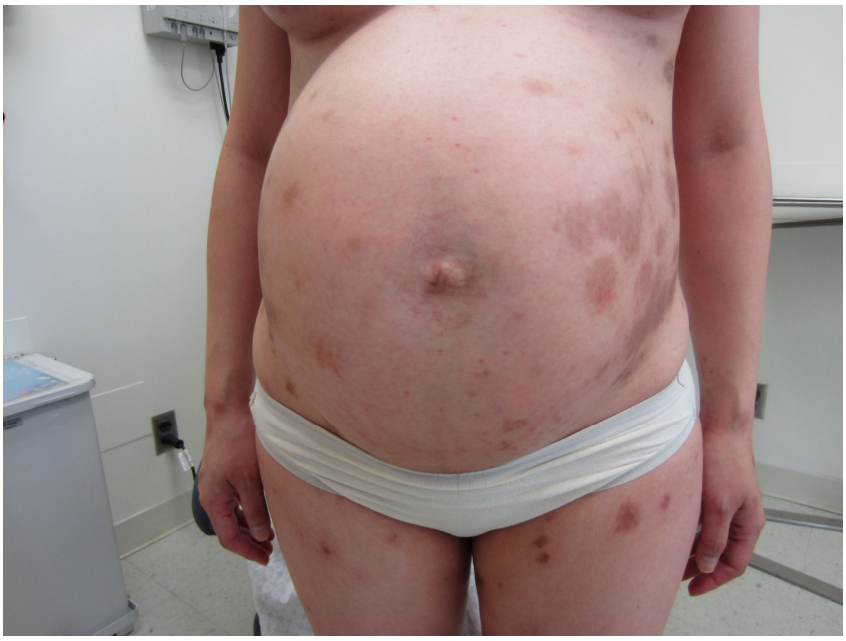
Impetigo Herpetiformis

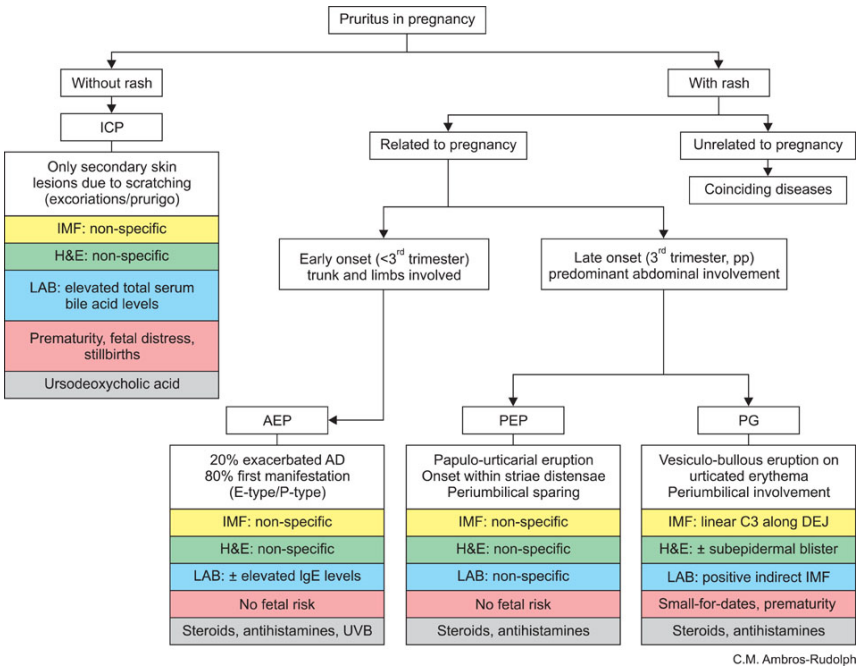
- Treatment
  - Topical steroids for limited disease or as adjunct therapy
  - Systemic corticosteroids: High-dose steroids (e.g. prednisone up to 60-80mg per day) and then slowly taper
  - Low-dose cyclosporine: 2-3mg/kg/day
  - Infliximab
  - nbUVB
- Early delivery considered for symptomatic relief and for fetal safety

Namazi and Sadkhahfar, Dermatol Res Pract. 2018

Back to the Case

- Patient treated with one week course of cephalexin and started on topical steroids.
- Declined systemic steroids despite extensive discussion regarding the possible risk to the fetus.
- Disease well controlled on TMC 0.1% cream.
- She delivered a healthy baby boy at 40 weeks and 6 days.





Ambros-Rudolph, Ann Dermatol, 2011

Thank you!

- Questions? Please e-mail me at:
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- Special thank you to my Terri Shih, BS, my research fellow